Placental mesenchymal stromal cells seeded on clinical grade extracellular matrix improve ambulation in ovine myelomeningocele.

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Public Summary:
Purpose: Myelomeningocele (MMC) is the most severe form of spina bifida that results in a spectrum of clinical manifestations including hydrocephalus, paralysis, and bowel and bladder dysfunction. Fetal surgery to repair MMC in humans has some benefit, but most children are still unable to walk. In our experiments on sheep, applying mesenchymal stem cells to the spinal cord at the time of fetal surgery for spina bifida has allowed the lambs to walk. In this study, we tested whether placing stem cells on a tissue patch (extracellular matrix) would improve the treated lambs' ability to walk. Methods: We isolated mesenchymal stem cells from a second trimester placenta and placed them on the tissue patch. We created the myelomeningocele defect in the first fetal surgery and then repaired it with either the tissue patch alone or stem cells on the patch weeks later. After they were delivered, we assessed their ability to walk. Later we analyzed the spinal cords. Results: Lambs repaired with the stem cells and tissue patch had an improved ability to walk compared to those repaired with the tissue patch only. After examining the spinal cords of the lambs, those treated with stem cells had more normal looking spinal cords and had more large neurons than the tissue patch only. Conclusion: We have demonstrated better motor function with application of stem cells than when a tissue patch alone is used for fetal surgical repair of myelomeningocele in sheep. Using the tissue patch alone helps to preserve the architecture of the spinal cord, however adding stem cells appears to help the repair by preserving large neurons. Based on these promising results in sheep, we plan a future clinical trial to determine if improvements in motor function persist in humans.

Scientific Abstract:
PURPOSE: The purpose of this study was to investigate the effects of placental mesenchymal stromal cells (PMSCs) seeded on a clinical grade porcine small intestinal submucosa (SIS)-derived extracellular matrix (ECM) on hindlimb motor function in an ovine fetal repair model of myelomeningocele (MMC). METHODS: MMC defects were surgically created in 21 fetuses at median gestational age 78 (range 76-83) days. Fetuses were randomly assigned to repair 25days later with ECM only or PMSC-ECM. Surviving fetuses were delivered at term. Motor function was evaluated using the Sheep Locomotor Rating (SLR) scale (0-15). Histologic analysis of the spinal cord (SC) was completed. RESULTS: Fetal viability was 71%. 5 of 8 (63%) lambs repaired with PMSC-ECM ambulated independently versus only 1 of 6 (17%) repaired with ECM only (p=0.04, chi(2) test). SLR scores and large neuron densities were higher in the PMSC-ECM group. The cross-sectional areas of the SC and the gray matter were equally preserved. CONCLUSIONS: Fetal repair of MMC with PMSCs seeded on SIS-ECM improves hindlimb motor function in lambs. Using ECM helps to preserve the architecture of the SC, but adding PMSCs improves the lamb's ability to walk and increases large neuron density. Clinical studies are needed to show benefits in humans. LEVELS OF EVIDENCE/TYPE OF STUDY: Basic Science.